Film-shaped mucoadhesive administration forms for administration of cannabis agents

The present invention relates to film-shaped, mucoadhesive administration forms which have a content of cannabis agents and which are suitable for administration of cannabis agents for therapeutic purposes. The invention further relates to the use of the said administration forms for treating conditions of disease in humans or animals.

The components of the Indian hemp plant (Cannabis sativa L.) have numerous pharmacological effects, of which the psychotropic effect is most widely known. Apart from this, cannabis components also have anti-emetic, anticonvulsive, muscle-relaxing, analgesic, sedative and appetite-increasing effects.
Because of the psychotropic or euphorizing effect and the dependency potential associated therewith, the therapeutic application of cannabis components is subject to severe restrictions.

It has long been known that cannabis components can be used with good effect for treating insomnia, neuralgias, painful rheumatism as well as gastric and intestinal disorders. A favourable therapeutic effect of cannabis components has furthermore been observed for the following indications:

Conditions of pain in cases of carcinosis and as a result of chemotherapy; conditions of pain and "wasting" syndrome in connection with AIDS; nausea and vomiting as side effects of a chemotherapy as well as in connection with AIDS or hepatitis; neuropathic pain; anorexia or cachexia,

especially in connection with AIDS or carcinosis in the advanced stages.

Paralytic symptoms in connection with multiple sclerosis or traumatic transverse lesions; dystonic motor disturbance; bronchial asthma; epileptic attacks or generalized epilepsia; withdrawal symptoms in connection with alcohol dependence, benzodiazepine dependence and opiate dependence; Parkinson's disease; dementia, especially Morbus Alzheimer; nausea; arthritis; glaucoma; migraine; dysmenorrhoea.

At present, only the synthetically produced cannabis agent R-(6a,10a)-Δ-9-tetrahydrocannabinol (Dronabinol) is marketable. This isomer of tetrahydrocannabinol (THC) is sold under the product name Marinol; this medicament is administered orally in the form of capsules. Marinol is used for treating severe loss of weight in AIDS patients and cancer patients who as a result of chemotherapy suffer from heavy vomiting.

Apart from the aforementioned THC isomer, cannabis extracts and cannabis oils for therapeutic treatment purposes are also suitable. Application is usually effected via the oral route, e.g. in the form of capsules.

Cannabis extracts contain as pharmacologically active ingredients tetrahydrocannabinol (predominantly Δ-9-tetrahydrocannabinol, in small proportion: Δ-8-tetrahydrocannabinol), cannabidiol, cannabinol and cannabichromen. These active agents are also called cannabinoids (see the list "The Merck Index", 12th ed., 1996, page 285, No. 1794, as well as page 1573, No. 9349).

Oral administration of cannabis agents, especially of R-(6a,10a)-Δ-9-tetrahydrocannabinol, in the form of capsules, tablets, pills or other solid, oral administration forms, or in the form of orally administered liquid preparations is disadvantageous for a variety of reasons:

- Since on use of the aforementioned administration forms, the absorption of the active agent takes place in the gastrointestinal tract, the time of onset of action is delayed. This is disadvantageous especially with respect to the indications mentioned, which generally require a quick onset of action (e.g. pain therapy).
- Cannabis agents are at least partially degraded and inactivated during the passage through the stomach and intestines under the influence of acid and enzymes, so that only part of the administered dose is absorbed and is systemically available.
- In this connection, unwanted plasma peak values may occur which are frequently the cause of side effects.
- In addition, after oral administration a significant portion of the active substance is already metabolised during the first passage through the liver ("first pass effect").

These disadvantages are particularly important with respect to the acceptance with which these medicaments are met in the above indicated indications. With the mentioned oral administration forms it is in addition of disadvantage that patients, in a particular given situation, regard the extended retention e.g. of a tablet or capsule (filled with an oily solution) in the mouth as particularly unpleasant.

It was therefore the object of the present invention to provide an administration form for the administration of cannabis agents which is free from the above-described

disadvantages and which stands out in particular for its improved acceptance and compliance, as well as for advantageous pharmacokinetic properties, especially for a rapid onset of action.

This object is achieved by a film-shaped, mucoadhesive administration form having a content of at least one active agent from the group of the cannabis agents, according to claim 1; further, preferred embodiments are described in the subclaims.
The object is furthermore achieved by the use of the film-shaped, mucoadhesive administration forms according to the invention in the treatment of diseases and symptoms.

The administration forms according to the invention are applied, preferably in the form of thin, small flat pieces or wafer-shaped objects ("wafers"), to the oral mucosa where they adhere because of their mucoadhesive properties. Application to the oral mucosa is preferably sublingual or buccal. Furthermore, other mucosal surfaces may also be taken into consideration as application site, e.g. the nasal mucosa.

During the period of application, the cannabis agent(s) contained in the administration form are released into the surrounding saliva and are subsequently absorbed by the oral mucosa (i.e. transmucosally). In the contact area of the application surface, the active agent may also be released directly from the administration form to the oral mucosa. During application, the administration form absorbs saliva and the active substance contained therein gets to the outside by diffusion.

It is advantageous in this connection that the active agent is released into the saliva after only a short time lag, so

that the saliva-active agent mixture immediately reaches all areas of the oral mucosa, where it can be absorbed. The amount of saliva in which the released active agent is dissolved or dispersed per unit of time is relatively small and there occurs no hypersalivation so that swallowing of the active agent (involving the mentioned disadvantages of gastrointestinal absorption) is largely excluded.
Since active agent absorption takes place by circumventing the gastrointestinal route, the above-described disadvantages (delayed onset of action, "first pass effect") of other oral administration forms (e.g. tablets) are avoided.

With the administration forms of the invention, compliance is increased as well, since application thereof requires no special discipline. Due to their small layer thickness the application of the film-shaped administration forms is generally not felt to be unpleasant by the treated persons.

According to a preferred embodiment, the administration forms of the invention comprise a polymer matrix which serves as active agent reservoir and has mucoadhesive properties. At least one layer or at least one surface of the administration form possesses mucoadhesive properties. The administration form may consist of one single layer or comprise a plurality of layers. In the case of a multilayer structure, at least one of the layers contains active agent(s).

In the simplest case, an administration form is made up of a mucoadhesive, preferably monolayer polymer matrix containing one or more cannabis agents. The active agent(s) may be present in the administration form in dissolved, dispersed or emulsified form.

The polymer matrix preferably contains one or more polymers which are water-soluble and/or swellable in aqueous media. By selecting such polymers, it is possible to influence the mucoadhesive properties and the release behaviour.

Polymers of the following group are particularly suitable as water-soluble or swellable polymers: starch and starch derivatives, dextran; cellulose derivatives, such as carboxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl ethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose or propyl cellulose; polyacrylic acid, polyacrylates, polyvinyl pyrrolidones, polyethylene oxide polymers, polyacrylamides, polyethylene glycol, gelatine, collagen, alginates, pectins, pullulan, tragacanth, chitosan, alginic acid, arabinogalactan, galactomannan, agar-agar, agarose, carrageenan, and natural gums.

The polymer portion is preferably 5 to 95%-wt, especially preferably 15 to 75%-wt, relative to the dry matter of the administration form.

According to a preferred embodiment, the administration forms according to the invention contain a cannabis extract or a cannabis oil, preferably in an amount of 0.5 to 50%-wt, especially preferably in an amount of 1 to 30%-wt. Processes for the manufacture of pharmaceutically acceptable cannabis extracts or cannabis oils are known to those skilled in the art.

The invention furthermore comprises administration forms of the mentioned type containing at least one cannabinoid active agent from the group consisting of tetrahydrocannabinol, cannabinol, cannabidiol, and

cannabichromen. Tetrahydrocannabinol, especially R-(6a,10a)-Δ-9-tetrahydrocannabinol, is particularly preferred as active agent. The cannabinoid active agents may be of natural, partially synthetic or synthetic origin. The active substance content preferably amounts to 0.1 to 20%-wt, especially preferably 0.5 to 10%-wt, relative to the dry matter of an administration form.
An individual administration form preferably contains 0.5 to 20 mg, especially preferably 1 to 10 mg of active agent, e.g. tetrahydrocannabinol.
Optionally, the administration forms according to the invention may contain one or more additives from the following groups: fillers, colourants, flavourings, aromatics, odorous substances, emulsifiers, plasticizers, sweeteners, preservatives, permeation-enhancing substances, pH regulators and antioxidants. Substances suitable for this purpose are in principle known to the skilled artisan.

It is of particular advantage to add flavourings, odorous substances and aromatics, either alone or in combination. It is, for example, possible to improve the impression of the taste by adding a refreshing flavouring (e.g. menthol, eucalyptol). This simultaneously enables inconspicuous intake of the medicament as it smells like a usual refreshment sweet. It additionally contributes to improving compliance.
Especially suitable are, for example, flavourings and aromatics from the group comprising menthol, eucalyptol, limonene, phenyl ethanol, camphene, pinene, seasoning aromatics such as n-butyl phthalide or cineol, as well as eucalyptus oil and thyme oil, methyl salicylate, turpentine oil, camomile oil, ethyl vanillin, 6-methyl coumarin, citronellol, and acetic acid n-butyl ester.

The inventive administration forms containing cannabis agents are film-shaped, i.e. of a thin and flat shape, for example in the form of thin, small flat pieces or small wafers. These film-shaped plates may be of various geometric shapes, e.g. circular, ellipsoid or elongated. Their thickness preferably amounts to 0.01 to 2 mm; with particular preference it is in the range of 0.05 to 0.5 mm. To avoid a foreign body sensation, the layer thickness should be as small as possible (preferably smaller than 0.2 mm).

To achieve special effects, the administration forms according to the invention may have a bilayer or monolayer structure. The individual layers may differ in terms of one or more of the following parameters: polymer composition, active substance content, active substance concentration, content of additives.

Due to the already mentioned properties, the cannabis agents-containing administration forms according to the invention can be employed to advantage in the treatment of diseases or symptoms, especially in cases of:
conditions of pain in cases of carcinosis and as a result of chemotherapy; conditions of pain and "wasting" syndrome in connection with AIDS; nausea and vomiting, especially nausea and vomiting as side effects of a chemotherapy as well as in connection with AIDS or hepatitis; neuropathic pain; anorexia or cachexia, especially in connection with AIDS or carcinosis in the advanced stages; paralytic symptoms in connection with multiple sclerosis or traumatic transverse lesions; dystonic motor disturbance; bronchial asthma; epileptic attacks or generalized epilepsia; withdrawal symptoms in connection with alcohol dependence, benzodiazepine dependence and opiate dependence; Parkinson's disease; dementia, especially Alzheimer's

disease; nausea; arthritis; glaucoma; migraine; dysmenorrhoea.